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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/642,974	08/18/2003	Martin Michaelis	DEAV20020064US NP	3394

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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
11/21/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/642,974	MICHAELIS ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14,16 and 17* is/are pending in the application.

4a) Of the above claim(s) *13,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Applicant's request for withdrawal of the restriction between Group I-III is found persuasive. Accordingly, the restriction requirement between Group I-III issued on 12/07/06 is withdrawn. In addition, upon further consideration, the examiner's election of species requirement among compounds of the formula I is withdrawn.

2. However, the election of species requirement among generic "pain" is considered proper because chronic pain due to inflammatory pain or postoperative pain or cancer pain (nociceptive pain) differs from neuropathic pain that caused by abnormalities in the nerves, spinal cord or brain. Furthermore, treatment of neuropathic pain differs from the treatment of nociceptive pain. Acknowledgement is made of applicant's election of "pain following injuries" as the elected species. Claims 2-12 and 14 read on the elected species.

3. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

4. Claims 2-12 and 14 are currently pending for prosecution on the merits.

5. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2-12 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the specific pain (for example pain associated with osteoarthritis or rheumatoid arthritis) with the formula I, does not reasonably provide enablement for treating pain (or an acute pain) with compounds represented by the formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The invention relates to a method of treatment of pain with IkB-kinase inhibitor compounds represented by the formula I.

The instant invention embraces the therapeutic treatment of all types of pain that may have different underlying mechanism, including pain due to inflammatory pain or postoperative

pain, neuropathic pain, cancer pain and idiopathic pain, more specifically pain associated with musculoskeletal disease, menstruation pain, arthritic pain, pain associated with intestinal inflammation, pain associated with cardiac muscle inflammation, pain associated with multiple sclerosis, neuritic pain, neuropathic pain, pain associated with carcinoma and sarcoma, pain associated with AIDs, pain associated with chemotherapy, amputation pain, headache, trigeminal neuralgia, post-operative pain, pain associated with gout, pain following jaw-bone surgical intervention and etc...

It is generally recognized in the art that pain is a complex subjective phenomenon comprised of a sensation indicating real or potential tissue damage and the affective response this generates; and classified into nociceptive, deafferetation and psychogenic pain depending upon their different underlying etiology and pathophysiology (The Merck Manual, Fifteenth Edition, 1987, pp1340-1356). For example, chronic pain due to inflammatory pain or postoperative pain or cancer pain (nociceptive pain) differs from neuropathic pain that caused by abnormalities in the nerves, spinal cord or brain. Also, treatment of neuropathic pain differs from the treatment of nociceptive pain.

Because of their different etiology, pathophysiology, diagnosis and treatment modality, it is known that no examples exist for efficacy of a single product against all types of chronic pain. The existence of such a "silver bullet" is contrary to our present understanding of pharmacology. Thus, it is beyond the skill of pharmacologists today to get an agent to be effective against all types of chronic pain.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed

tests that are highly predictive for the treatment of all of chronic pain by the administration of the instant drug combination. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

As discussed above, the instant claims embrace the therapeutic treatment of all types of chronic pain that may have different underlying mechanism, for example (i) pain due to inflammatory pain or postoperative pain, (ii) neuropathic pain, (iii) cancer pain and (iv) idiopathic pain.

The instant specification discloses pain assay (pages 33-40) to test the compound represented by the formulas in vivo and discloses that the compound of 13 (N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)_1H-indole-5-carboxamide) is effective in reducing pain associated with joint or knee inflammation. However, there is no demonstrated correlation that the tests and results apply to all disease conditions associated with pain embraced by the instant claims.

As discussed above, it is not known yet that a single agent is effective against all types of pain. For instance, nueropathic pain differs from acute nociceptive pain, which is caused by the normal activation of neural pathways in response to pain-initiating stimulus, and acquires different types of treatment as to the acute nociceptive pain (See "Neuropathic Pain: Diagnosis, Treatment, and the Pharmacist's Role in Patient Care, Pharmacy Times, 2005). Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of said IkB-kinase inhbitors.

In view of limited numbers of working examples, the insufficient amount of guidance present in the specification, the nature of the invention, the state of art, the breadth of the claim and the relative skills of the artisan and the predictability of the pharmaceutical art where many specific differences or different physicochemical properties are existed among unrelated structural compounds would take "undue painstaking experimentation" to practice the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

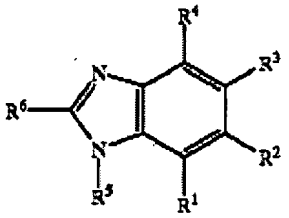
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

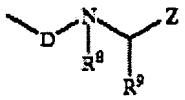
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ritzeler et al. (US 6358978 B1).

Ritzeler discloses the compounds of formula I  having IkB kinase inhibitor activity wherein R1, R2, R3 and R4 is radical of formula II



for the treatment of rheumatoid arthritis and osteoarthritis (conditions characterized by inflammation of joint, usually accompanied by pain, swelling and stiffness).

The claims differ from the reference by reciting a specific species and a more limited genus than the reference. However, it would have been obvious to one having ordinary skill in the art at the time of the invention to select any of the genus taught by the reference, including those of the claims, because an ordinary artisan would have the reasonable expectation that any of the species of the genus would have similar properties and, thus, the same use as the genus as a whole, in absence evidence to the contrary.

Thus, one would have been motivated to make such modification to extend the usage of Ritzeler's composition or compound(s) to treat patient suffering from rheumatoid arthritis and

osteoarthritis pain and inflammation. This modification would have been obvious because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Response to Arguments

8. Applicant's arguments filed 09/29/06 have been fully considered but they are not persuasive.

Applicant's argument in the response takes the position that the Action provides no evidence or technical reasoning to show that one of ordinary skill in the art would not be able practice the claimed invention. Applicant asserts that the Patent Office bears the "initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification".

This argument is not found persuasive. Contrary to the appellant's allegation, the examiner have cited documents ("Neuropathic Pain: Diagnosis, Treatment, and the Pharmacist's Role in Patient Care, Pharmacy Times, 2005 and The Merck Manual, Fifteenth Edition, 1987, pp1340-1356) to support the examiner's position in determining why the instant invention does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

As discussed above, nueropathic pain differs from acute nociceptive pain, which is caused by the normal activation of neural pathways in response to pain-initiating stimulus, and acquires different types of treatment as to the acute nociceptive pain. Thus, the skilled artisan would have not expected based on the instant in vivo study involving the efficacy of compound

of 13 (N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide in reducing pain associated with joint or knee inflammation that the administration of said compound would be able to treat all types of chronic pain that may have different underlying mechanism, for example (i) pain due to inflammatory pain or postoperative pain, (ii) neuropathic pain, (iii) cancer pain and (iv) idiopathic pain.

The examiner respectfully points out that in the determination of enablement one must take into account the guidance of the specification and the working examples (if any) presented in the specification. Applicant has not provided sufficient guidance to make the reasonable correlation that an inordinate number of compound(s) encompassed by the instant formula (I) would work similar to the tested compounds of the formula (I) when E is CH, 13 (N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide. Applicant has not specifically described the compounds tested in the assays (only two compounds, N-[(S)-2-dipheylamino-2-(5-oxo-4,5-dihydro[1,3,4]oxadiazol-2-yl)ethyl]-2-(2-methylaminopyrimidin-4-yl)-1H-indole-5-carboxamide and N-[(S)-1-carbamoyl-2-diphenylaminoethyl-2-(2-methylaminopyrimidin -4-yl)-1H-benzimidazole-5-carboxamide), they have not correlated the structure of the compounds tested with their relative activity in said assays and they have not tested the compounds in any chronic pain as claimed. Thus, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of working examples, and the insufficient amount of guidance

present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use for treatment of " a disease mediated by p38" with the compounds of Formula I that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

Applicant's argument in the response takes the position that Ritzeler does not teach or suggest that any of compounds disclosed therein are useful to treat pain. Applicant asserts that Ritzeler discloses substituted benzimidazoles for use in the prevention of treatment of Alzheimer's disease, asthma, cachexia, psoriasis and multiple sclerosis, for example, in which increased activity of NFkB is involved; and that there is no suggestion or motivation from Ritzeler that why one of ordinary skill in the art at the time of the present invention would select the applicant's recited subgenus to treat the instant claimed pain.

This argument is not found persuasive. Unlike the applicant's argument, at the time of the invention was made, it was known that NFkB inhibitor is useful for the treatment of inflammation or pain associated with inflammation, for example osteoarthritis, rheumatoid arthritis, ankylosing spondilytis (see USP 7053120, especially "Background", column 3, lines 64-67 and column 4, line 59 through column 5, line 2; USP 6596770). Thus, the skill artisan would have expected that the Ritzeler's compounds of the formula I would be useful in the treatment of chronic pain.

Conclusion

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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